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## **REMARKS**

### **I. Petition for Extension of Time**

Applicants herewith petition the Commissioner for Patents to extend the time for response to the Office action mailed 27 March 2006 for three months from 27 June 2006 to 27 September 2006. Authorization is given to charge the extension of time fee of \$1020.00 (37 C.F.R. §§1.136 and 1.17) to Deposit Account No. 23-1703. Any deficiency or overpayment should be charged or credited to the above numbered deposit account.

### **II. Examiner Interview**

On behalf of the Applicants, the undersigned Attorney wishes to thank the Examiner for the courtesy of the telephonic interview that took place on 14 March 2006. Applicants submit that the Examiner-Initiated Interview Summary provides a complete written statement in satisfaction of 37 C.F.R. §1.133(b) as to the substance of the interview with regard to the merits of the subject application.

### **III. Claim Rejections – 35 U.S.C. §103(a)**

#### **A. US 6,245,351 to Nara et al. ("Nara") in view of US 5,225,202 to Hodges et al. ("Hodges")**

Claims 1, 3, 6-8, 12-18, 20 and 25-29 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nara in view of Hodges.

##### **1. The claimed invention**

The active ingredient of the claimed dosage form is an omeprazole compound. It is established in the literature that the target site of omeprazole is the small intestine where the pH is near neutral (specification, p. 2, lines 4-9). The core of the claimed dosage form contains a sufficiently large amount of an alkaline agent, i.e., approximately 10 to 35 % by weight of the core material excluding the weight of an optional starter seed. The alkaline agent acts to neutralize acidic gastric fluids adsorbed through the semipermeable membrane while the dosage form, which is not enteric-coated, passes through the stomach en route to the small intestine.

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2. Nara does not teach the desirability to obtain stable acid labile compositions.

The claimed invention is especially concerned with the preparation of a stable acid labile formulation especially since the core containing the omeprazole compound is not protected with an enteric coating.

While it is true that Nara discloses a broad range of possible active ingredients (col. 3, lines 35-63), including omeprazole and lansoprazole, Nara is silent with respect to the unique problems associated with the formulation of dosage forms having an acid-labile substance as the active ingredient. This is no surprise since Nara is concerned with opiod compounds which are expressly preferred by Nara (col. 3, line 65).

The Examiner appears to agree since the statement "because Nara teaches the desirability to obtain a stable acid labile composition" which appeared on page 6, lines 1-2, of the previous Office Action, mailed 17 August 2005, is noticeably missing from the outstanding Office Action, mailed 27 March 2006.

3. Nara does not teach the amount of alkaline additive in the core.

Nara discloses a drug-containing core which is not enteric-coated and which optionally includes a lubricant, e.g., talc. On page 4 of the Office Action, the Examiner acknowledges that "Nara does not explicitly teach the amount of alkaline additive present in the core".

4. The omeprazole compound of the claimed invention would be degraded and rendered therapeutically ineffective if released at the pH values taught by Hodges.

The Examiner relies on the disclosure by Hodges of an enteric-coated tablet core containing the active and a buffering agent within the range of from about 1 to about 20% by weight (col. 3, lines 20-26). The Examiner concludes, therefore, that it would have been obvious to use an alkaline additive in an amount taught by Hodges to obtain a stable acid-labile composition. Applicants respectfully disagree.

It has been established that the primary reference to Nara does not teach the desirability to obtain stable acid labile compositions, in particular, formulations containing an omeprazole compound as the active.

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The secondary reference to Hodges is admittedly related to formulations containing a medicament that is sensitive to a low pH environment of less than 3. However, it is an express teaching of Hodges that the formulations are designed to have good drug release properties at pH greater than 3 (Abstract; col. 1, lines 6-12). The only disclosed examples of such a medicament are "pravastatin, erythromycin, ddI (dideoxyinosine), digoxin, pancreatin, ddA, ddC, and the like" (col. 3, lines 16-21). All of the working examples, i.e., Examples 1 and 2, are directed to compositions containing pravastatin.

Hodges does not teach nor disclose and is apparently not concerned with acid labile compounds such as omeprazole and the unique problems associated with the preparation of dosage forms containing an omeprazole compound as the active. Preparation of an omeprazole formulation in accordance with Hodges where the omeprazole compound is released in a low PH environment, e.g., pH > 3, would be disastrous for the omeprazole compound. Specifically, the omeprazole compound of the claimed invention would be degraded in the pH environments disclosed by Hodges. In this regard, the Examiner's attention is directed to the Information Disclosure Statement, filed 27 February 2003, and the article cited therein, Pilbrant, Å, et al., Development of an oral formulation of omeprazole, Scandinavian Journal of Gastroenterology, 20 (suppl. 108):113-120 (1985). On page 113 of the article which is attached hereto for the Examiner's convenience, the authors state that the rate of degradation of omeprazole proceeds with a half-life of less than 10 minutes at pH values below 4.

In contrast to the low pH environments disclosed by Hodges, it is established in the literature that the target site of omeprazole is the small intestine where the pH is near neutral (specification, p. 2, lines 4-9). On page 113 of the same article by Pilbrant et al., it is stated that the half-life degradation of omeprazole at pH 6.5 is 18 hours.

Accordingly, reading just the Abstract of Hodges, the skilled artisan contemplating the preparation of a stable formulation containing an omeprazole core which is not protected by an enteric coating would disregard Hodges as inappropriate and incompatible for such a formulation.

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**5. There is no motivation to combine Nara and Hodges.**

The primary reference to Nara does not teach the desirability to obtain stable acid labile compositions. Hodges discloses pharmaceutical formulations which release in low pH environments, e.g., pH > 3, which would render the claimed dosage form unstable and resulting in a rapid degradation of the omeprazole compound.

Therefore, there would have been no motivation at the time the claimed invention was made to combine Nara and Hodges. The low pH environments disclosed by Hodges may be suitable for pravastatin, an HMG CoA reductase inhibitor, used in cardiovascular medicines. However, as indicated by the Pilbrant et al. article, the omeprazole compound of the claimed invention would rapidly degrade in such low pH environments.

Whether taken alone, or in combination, neither Nara nor Hodges discloses or suggests the claimed omeprazole formulation which is not enteric coated but which advantageously reaches the neutral pH environment of the small intestine where it is released and absorbed to provide the intended therapeutic benefit.

For all of the foregoing reasons, a *prima facie* case of obviousness has not been established. Accordingly, withdrawal of the §103 rejection of claims 1, 3, 6-8, 12-18, 20 and 25-29 based on the combination of Nara and Hodges is requested.

**B. Nara, Hodges and US 4,795,644 to Zentner ("Zentner") or  
US 6,013,281 to Lundberg et al. ("Lundberg")**

Claims 9 and 10 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nara in view of Hodges and Zentner or Lundberg.

Zentner is cited by the Examiner for the alleged disclosure of sodium mono- or di-phosphate as a pH modifying agent. Lundberg is cited for the disclosure of arginine as an alkaline reacting compound.

Claims 9 and 10 are directly or indirectly dependent on claim 1. For all of the reasons given in Section III(A), above, there would have been no motivation at the time the claimed invention was made to combine Nara and Hodges to arrive at the claimed invention, for example as defined by claim 1. Neither Zentner nor Lundberg overcomes the failure of the combination of Nara and Hodges to establish a *prima facie* case of obviousness. Accordingly, withdrawal of the §103 rejection of claims 9 and 10 is requested.

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**C. Nara, Hodges and WO 98/54171 ("Cotton")**

Claims 4, 5 and 23-26 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nara in view of Hodges and Cotton.

As stated by the Examiner on page 5 of the Office Action, Cotton is cited for the disclosure of the magnesium salt of S-omeprazole as an active ingredient. Applicants submit that Cotton does not overcome the deficiencies of Nara and Hodges to establish a *prima facie* case of obviousness for the reasons given in Section III(A). Withdrawal of the §103 rejection of claims 4, 5 and 23-26 is requested.

**CONCLUSION**

Applicants have made a good faith attempt to respond to the Office Action. It is respectfully submitted that claims 1, 3-10, 12-18, 20 and 23-29 are in condition for allowance, which action is earnestly solicited.

Any fees due in connection with this response should be charged to Deposit Account No. 23-1703.

Dated: 15 September 2006

Respectfully submitted,



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Attachment: p.113 of Pilbrant, Å, et al., Development of an oral formulation of omeprazole, Scandinavian Journal of Gastroenterology, 20 (suppl. 108):113-120 (1985).

# Development of an oral formulation of omeprazole

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Pilbrant Å, Cederberg C. Development of an oral formulation of omeprazole. *Scand J Gastroenterol* 1985;20(suppl 108):113-120.

Omeprazole has a low water solubility and is chemically labile in an acid environment. In the formulation of an oral dosage form of omeprazole the possibilities of dissolution rate limited absorption and preabsorption degradation must be kept in mind. A water suspension of omeprazole was tested in a pilot bioavailability study. The suspension was given to six healthy, fasting volunteers on two occasions - together with sodium bicarbonate solution and together with the same volume of water. When the suspension was given with water the bioavailability was reduced by about 50 % owing to preabsorption degradation. In another bioavailability study the slowest of three granule formulations with differing *in vitro* dissolution rates showed a reduced extent of absorption.

A controlled-release pellet formulation (enteric-coated) was formulated and tested in a series of bioavailability studies. A single dose given with food resulted in a delayed absorption and possibly lower bioavailability than under fasting conditions. When the granules were given on an empty stomach before the morning meal the length of time between dosage and meal was of no importance. Concomitant administration of a liquid antacid had no influence on the bioavailability of omeprazole.

**Key-words:** Bioavailability; controlled release; dosage form; enteric coating; omeprazole; stability

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## Introduction

Omeprazole (Figure 1) is a substituted benzimidazole which selectively inhibits the proton pump in the gastric mucosa (1, 2). Omeprazole is very slightly soluble in water, but is very soluble in alkaline solutions as the negatively charged ion. It is an ampholyte with  $pK_a = 4$  (pyridinium) and 8.8 (benzimidazole).

Omeprazole degrades very rapidly in water solutions at low pH-values. Figure 2 shows a plot of the logarithm of the observed rate constant for degradation as a function of pH. In each experiment, the initial, pseudo-first-order rate of degradation was calculated from the amount of unchanged omeprazole in buffer solutions (3). The rate of degradation proceeds with a half-life of less

than 10 minutes at pH-values below 4. At pH 6.5 the half-life of degradation is 18 hours; at pH 11 about 300 days.

Preformulation studies have shown that moisture, solvents and acidic substances have a deleterious effect on the stability of omeprazole and should be avoided in pharmaceutical formulations.

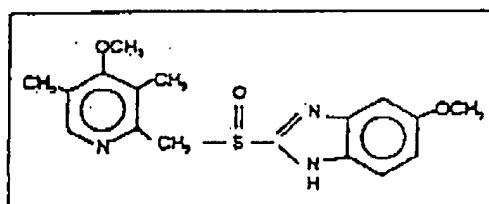


Figure 1. Omeprazole, H 168/68, 5-methoxy-2-[(4-methoxy-3,3-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole.